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(54) **Spiro [1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine for use in the treatment of psychotic and intellectual impairment disorders**

Spiro [1-azabicyclo[2.2.2]octan-3,2'(3'H)-furo[2,3-b]pyridin zur Verwendung in der Behandlung von psychotischen und intellektuellen Störungen

Spiro [1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine pour le traitement des troubles psychotiques et intellectuels

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(56) References cited:
WO-A-97/05139

- **NORDVALL G ET AL:**
"3-(2-Benzofuranyl)quinuclidin-2-ene derivatives: novel muscarinic antagonists"
JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 39, no. 17, 1996, pages 3269-3277, XP002123211 ISSN: 0022-2623

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Description

TECHNICAL FIELD

[0001] This invention relates to novel spiroazabicyclic heterocyclic amines or pharmaceutically acceptable salts thereof, processes for preparing them, pharmaceutical compositions containing them and their use in therapy. A further object is to provide active compounds which are potent ligands for nicotinic acetylcholine receptors (nAChR's).

BACKGROUND OF THE INVENTION

[0002] The use of compounds which bind nicotinic acetylcholine receptors in the treatment of a range of disorders involving reduced cholinergic function such as Alzheimer's disease, cognitive or attention disorders, anxiety, depression, smoking cessation, neuroprotection, schizophrenia, analgesia, Tourette's syndrome, and Parkinson's disease has been discussed in McDonald et al. (1995) "Nicotinic Acetylcholine Receptors: Molecular Biology, Chemistry and Pharmacology", Chapter 5 in Annual Reports in Medicinal Chemistry, vol. 30, pp. 41-50, Academic Press Inc., San Diego, CA; and in Williams et al. (1994) "Neuronal Nicotinic Acetylcholine Receptors," Drug News & Perspectives, vol. 7, pp. 205-223.

[0003] US Patent 5,468,875 discloses N-alkylcarbamic acid 1-azabicyclo[2.2.1]hept-3-yl esters which are centrally active muscarinic agents useful in the treatment of Alzheimer's disease and other disorders.

[0004] N-(2-alkoxyphenyl)carbamic acid 1-azabicyclo[2.2.2]octan-3-yl esters are disclosed in Pharmazie, vol. 48, 465-466 (1993) along with their local anesthetic activity. N-phenylcarbamic acid 1-azabicyclo[2.2.2]octan-3-yl esters substituted at the *ortho* position on the phenyl ring are described as local anaesthetics in *Acta Pharm. Suecica*, 7, 239-246 (1970).

[0005] Furopyridines useful in controlling synaptic transmission are disclosed in WO 97/05139.

DISCLOSURE OF THE INVENTION

[0006]

- (*R*)-Spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo [2,3-b]pyridine] tartrate;

Pharmaceutical compositions

[0007] A further aspect of the invention relates to a pharmaceutical composition for treating or preventing a condition or disorder as exemplified below arising from dysfunction of nicotinic acetylcholine receptor neurotransmission in a mammal, preferably a human, comprising an amount of a compound of formula I, an enantiomer thereof or a pharmaceutically acceptable salt thereof, effective in treating or preventing such disorder or condition and an inert pharmaceutically acceptable carrier.

[0008] For the above-mentioned uses the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds of the invention are administered at a daily dosage of from about 0.1 mg to about 20 mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man, the total daily dose is in the range of from 5 mg to 1,400 mg, more preferably from 10 mg to 100 mg, and unit dosage forms suitable for oral administration comprise from 2 mg to 1,400 mg of the compound admixed with a solid or liquid pharmaceutical carrier or diluent.

[0009] The compounds of formula I, or an enantiomer thereof, and pharmaceutically acceptable salts thereof, may be used on their own or in the form of appropriate medicinal preparations for enteral or parenteral administration. According to a further aspect of the invention, there is provided a pharmaceutical composition including preferably less than 80% and more preferably less than 50% by weight of a compound of the invention in admixture with an inert pharmaceutically acceptable diluent or carrier.

[0010] Examples of diluents and carriers are:

- for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose;
- for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

[0011] There is also provided a process for the preparation of such a pharmaceutical composition which comprises mixing the ingredients.

Utility

[0012] A further aspect of the invention is the use of a compound according to the invention, an enantiomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of one of the below mentioned diseases or conditions; and a method of treatment or prophylaxis of one of the above mentioned diseases or conditions, which comprises administering a therapeutically effective amount of a compound according to the invention, or an enantiomer thereof or a pharmaceutically acceptable salt thereof, to a patient.

[0013] Compounds according to the invention are agonists of nicotinic acetylcholine receptors. While not being limited by theory, it is believed that agonists of the α7 nAChR (nicotinic acetylcholine receptor) subtype should be useful in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders,

and have advantages over compounds which are or are also agonists of the α4 nAChR subtype. Therefore, compounds which are selective for the α7 nAChR subtype are preferred. The compounds of the invention are indicated as pharmaceuticals, in particular in the treatment or prophylaxis of psychotic disorders and intellectual impairment disorders. Examples of psychotic disorders include schizophrenia, mania and manic depression, and anxiety. Examples of intellectual impairment disorders include Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, and Attention Deficit Hyperactivity Disorder. The compounds of the invention may also be useful as analgesics in the treatment of pain (including chronic pain) and in the treatment or prophylaxis of Parkinson's disease, Huntington's disease, Tourette's syndrome, and neurodegenerative disorders in which there is loss of cholinergic synapses. The compounds may further be indicated for the treatment or prophylaxis of jetlag, for use in inducing the cessation of smoking, and for the treatment or prophylaxis of nicotine addiction (including that resulting from exposure to products containing nicotine).

[0014] It is also believed that compounds according to the invention are useful in the treatment and prophylaxis of ulcerative colitis.

Pharmacology

[0015] The pharmacological activity of the compounds of the invention may be measured in the tests set out below:

Test A - Assay for affinity at α7 nAChR subtype

[0016] [^{125}I]-α-Bungarotoxin (BTX) binding to rat hippocampal membranes. Rat hippocampi were homogenized in 20 volumes of cold homogenization buffer (HB: concentrations of constituents (mM): tris(hydroxymethyl)aminomethane 50; $MgCl_2$ 1; NaCl 120; KCl 5: pH 7.4). The homogenate was centrifuged for 5 minutes at 1000 g, the supernatant was saved and the pellet re-extracted. The pooled supernatants were centrifuged for 20 minutes at 12000 g, washed, and resuspended in HB. Membranes (30-80 µg) were incubated with 5 nM [^{125}I]-α-BTX, 1 mg/mL BSA (bovine serum albumin), test drug, and either 2 mM $CaCl_2$ or 0.5 mM EGTA [ethylene glycol-bis(β-aminoethylether)] for 2 hours at 21°C, and then filtered and washed 4 times over Whatman glass fibre filters (thickness C) using a Brandel cell harvester. Pretreating the filters for 3 hours with 1% (BSA/0.01% PEI (polyethyleneimine) in water was critical for low filter blanks (0.07% of total counts per minute). Nonspecific binding was described by 100 µM (-)-nicotine, and specific binding was typically 75%.

Test B - Assay for affinity to the α4 nAChR subtype

[0017] [^{3}H]-(-)-nicotine binding. Using a procedure modified from Martino-Barrows and Kellar (Mol Pharm (1987) 31:169-174), rat brain (cortex and hippocampus) was homogenized as in the [^{125}I]-α-BTX binding assay, centrifuged for 20 minutes at 12,000 x g, washed twice, and then resuspended in HB containing 100 µM diisopropyl fluorophosphate. After 20 minutes at 4°C, membranes (approximately 0.5 mg) were incubated with 3 nM [^{3}H]-(-)-nicotine, test drug, 1 µM atropine, and either 2 mM $CaCl_2$ or 0.5 mM EGTA for 1 hour at 4°C, and then filtered over Whatman glass fibre filters (thickness C) (pretreated for 1 hour with 0.5% PEI) using a Brandel cell harvester. Nonspecific binding was described by 100 µM carbachol, and specific binding was typically 84%.

Binding data analysis for Tests A and B

[0018] IC_{50} values and pseudo Hill coefficients (n_H) were calculated using the non-linear curve fitting program ALLFIT (DeLean A, Munson P J and Rodbard D (1977) Am. J. Physiol., 235:E97-E102). Saturation curves were fitted to a one site model, using the non-linear regression program ENZFITTER (Leatherbarrow, R.J. (1987)), yielding KD values of 1.67 and 1.70 nM for the [^{125}I]-α-BTX and [^{3}H]-(-)-nicotine ligands respectively. Ki values were estimated using the general Cheng-Prusoff equation:

$$K_i=[IC_{50}]/((2+([ligand]/[K_D])_n)_{1/n}-1)$$

where a value of n=1 was used whenever $n_H<1.5$ and a value of n=2 was used when $n_H\geq1.5$. Samples were assayed in triplicate and were typically ±5%. K_i values were determined using 6 or more drug concentrations. The compounds of the invention are compounds with binding affinities (K_i) of less than 1000 nM in either Test A or Test B, indicating that they are expected to have useful therapeutic activity.

[0019] The compounds of the invention have the advantage that they may be less toxic, be more efficacious, be longer acting, have a broader range of activity, be more potent, produce fewer side effects, are more easily absorbed or have other useful pharmacological properties.

EXAMPLES

[0020] Commercial reagents were used without further purification. Mass spectra were recorded using either a Hewlett Packard 5988A or a MicroMass Quattro-1 Mass Spectrometer and are reported as m/z for the parent molecular ion with its relative intensity. Room temperature refers to 20-25°C.

Preparation 1

Spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane]N-borane complex

[0021] A mixture of trimethylsulfoxonium iodide (16.10 g, 73.2, mmol) and a dispersion of sodium hydride (60% in oil. 3.00 g. 75.0 mmol) in anhydrous dimethyl sulfoxide was stirred at room temperature under nitrogen for 30 minutes. Quinuclidin-3-one (7.05 g, 56.3 mmol) was then added as a solid portionwise, and the resulting mixture was stirred at 65-70°C under nitrogen for 1 hour. The reaction mixture was cooled, water was added (200 mL), and the resulting solution was extracted with chloroform (3 x 200 mL). The chloroform extracts were combined, and back-extracted with water (4 x 200 mL). The chloroform layer was then dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] (6.51 g, 46.8 mmol, 83%) as a clear, colorless liquid. To a stirred solution of spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] (5.3 g, 38.1 mmol) in anhydrous tetrahydrofuran (100 mL) at 0°C was added dropwise a solution of borane in tetrahydrofuran (1.0 M, 38.1 mL, 38.1 mmol), and resulting solution was stirred at 0°C under nitrogen for 30 minutes. Brine (100 mL) was added cautiously to the reaction solution, and the resulting aqueous mixture was extracted with ethyl acetate (2 x 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the title compound (4.3 g, 28.1 mmol, 74%) as a white solid: electrospray MS 152 ([M-H]$^+$, 15).

Preparation 2

3-(2-Chloropyridin-3-ylmethyl)-3-hydroxy-1-azabicyclo [2.2.2]octane N-borane complex

[0022] A solution of phenyllithium (1.8 M in cyclohexane/ether [7:3], 167 mL, 0.3 mol, 3 eq.) was added via a cannula to anhydrous tetrahydrofuran (350 mL) at -60°C under a nitrogen atmosphere. Then, diisopropylamine (0.7 mL, 5mmol) was added dropwise, followed by a dropwise addition of 2-chloropyridine (28.4 mL, 0.3 mol, 3 eq.) over ten minutes. The resulting solution was stirred at -40°C under nitrogen for 1.5 hours. The solution was then cooled to -60°C, and a solution of spiro[1-azabicyclo[2.2.2]octane-3,2'-oxirane] N-borane complex (15.3 g, 0.1 mol) in tetrahydrofuran (75 mL) was added dropwise. The resulting reaction mixture was then stirred at -40°C under nitrogen. After 3 hours, a saturated solution of sodium bicarbonate (150 mL) was slowly added, followed by water (400 mL), and the resulting aqueous mixture was allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with ethyl acetate (3 x 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Column chromatography using silica gel and elution with ethyl acetate/hexanes [3:2] afforded the title compound as a tan solid (17.5 g, 65.6 mmol, 66%): electrospray MS 269 ([MH]$^+$ with ^{37}Cl, 10), 267 ([MH]$^+$ with ^{35}Cl, 26).

Preparation 2(b)

3-(2,4-Dichloropyridin-3-ylmethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane N-borane complex

[0023] The complex was prepared from 2.64 g (17.8 mmol) of 2,4-dichloropyridine and 1.37 g (8.95 mmol) of spiro[1-azabicyclo[2.2.2]octane-3,2'oxirane], providing 2.42 g (90%), m.p. 178-179°C (1:1 ethyl acetate-hexane).

Preparation 3

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b] pyridine] N-borane complex

[0024] 3-(2-Chloropyridin-3-ylmethyl)-3-hydroxy-1-azabicyclo[2.2.2]octane N-borane complex (17.4 g, 65.3 mmol) was dissolved in anhydrous N,N-dimethylformamide (500 mL), the resulting solution was cooled to 0°C under nitrogen, and a dispersion of sodium hydride (60% in oil, 6.55 g, 163 mmol, 2.5 eq.) was added portionwise. The resulting solution was stirred at room temperature under nitrogen for 16 hours. A saturated solution of ammonium chloride (50 mL) was then added at 0°C, followed by ice water (500 mL), and the resulting aqueous mixture was extracted with chloroform (4 x 125 mL). The organic extracts were combined, dried ($MgSO_4$), and evaporated under reduced pressure to afford an orange solid. Purification through a short column of silica gel eluting with chloroform/acetone [95:5 to 85:15], followed by stirring in hexanes (100mL) and filtration, provided a yellow solid (12.7 g, 55.2 mmol, 84%) of the title compound: electrospray MS 231 ([MH]$^+$, 65).

Preparation 4

3-(2-Methanesulfonyloxyethyl)-3-trimethylsilyloxy-1-azabicyclo[2.2.2]octane N-borane complex

(a) 2-(3-Hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid t-butyl ester

[0025] To a solution of diisopropylamine (6.7 mL) in tetrahydrofuran (THF) (20 mL) at 0° C was added n-butyllithium (2.3M in hexanes; 20 mL). The reaction mixture was stirred for 40 minutes and then cooled to -78°C. To this mixture a solution of t-butyl acetate (6.4 mL) in THF (10 mL) was added dropwise and stirring was continued for an additional 15 minutes. Quinuclidin-3-one (5 g) in THF (15 mL) was added to the mixture dropwise and the mixture was allowed to warm to 0°C over 1 hour. To this solution water (100 mL) was added, the solution

was extracted twice with chloroform and the combined extracts were washed once with brine. The resulting solution was dried over $MgSO_4$, filtered, and evaporated in vacuo to give 9.53 g of the subtitle compound as an off-white solid.

(b) 2-(3-Hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid methyl ester

[0026] Trifluoroacetic acid (40 mL) was added dropwise over 15 minutes to a solution of 2-(3-hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid t-butyl ester (15.7 g) in anhydrous dichloromethane (40 mL) at 0°C. The mixture was stirred for 24 hours at room temperature, then the solvent was evaporated under reduced pressure. The residue was dissolved in methanol (90 mL) and cooled in an ice bath. Concentrated sulfuric acid (9 mL) was added dropwise over 10 minutes, then the reaction mixture was stirred at room temperature. After 3 hours, the solution was poured into 100 mL of ice water, basified to pH 10 with saturated aqueous sodium carbonate solution, and extracted with chloroform (4 x 100 mL). The extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give a solid. Recrystallization from ethyl acetate provided 6.3 g of the tan crystalline subtitle compound.

(c) 2-(3-Hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid methyl ester N-borane complex

[0027] Borane in THF (1 M, 5.25 mL) was added dropwise over 20 minutes to a solution of 2-(3-hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid methyl ester (1 g) in anhydrous tetrahydrofuran (THF) (20 mL) stirred at 0°C. After 30 minutes, 20 mL of brine was added, stirring was continued for a further 30 minutes and the layers were then separated. The aqueous layer was extracted with ethyl acetate (2 x 20 mL), the organic layers were combined, and then dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residue was subjected to flash chromatography on silica gel (eluting with chloroform/acetone, 95:5) to give the title compound (900 mg) as an off-white solid.

(d) 3-Hydroxy-3-(2-hydroxyethyl)-1-azabicyclo[2.2.2] octane N-borane complex

[0028] Under an argon atmosphere, lithium borohydride (2 M in tetrahydrofuran, 2.6 mL, 5.2 mmol) was added over 5 minutes to a solution of 2-(3-hydroxy-1-azabicyclo[2.2.2]oct-3-yl)acetic acid methyl ester N-borane complex (1 g, 4.7 mmol) in anhydrous tetrahydrofuran (20 mL) and heated at reflux for 1 hour. The reaction was cooled (ice bath), quenched with water (5 mL) and saturated aqueous sodium bicarbonate (5 mL), stirred for 45 minutes at 0°C to room temperature, and extracted four times with ethyl acetate. The combined organic layers were dried ($MgSO_4$), evaporated under reduced pressure and triturated with ethyl ether to obtain the title compound (830 mg, 4.5 mmol, 95%) as a white solid.

(e) 3-Trimethylsilyloxy-3-(2-trimethylsilyloxyethyl)-1-azabicyclo[2.2.2]octane N-borane complex

[0029] Under an argon atmosphere, chlorotrimethylsilane (0.255 mL, 2 mmol) was added via syringe over 5 minutes to 3-hydroxy-3-(2-hydroxyethyl)-1-azabicyclo [2.2.2]octane N-borane complex (185 mg, 1 mmol) in dry 1-methylimidazole (1 mL) at 0°C. N-(trimethylsilyl) acetamide (262 mg, 2 mmol) was added in one portion, the reaction was stirred for 16 hours at room temperature and heated at 55-60°C for 3 hours. The mixture was cooled, poured into ice/water (5 g), and extracted four times with ether. The combined organic layers were washed four times with brine, dried ($MgSO_4$), evaporated under reduced pressure and purified by flash chromatography (eluting with hexane/ethyl acetate, 3:2) to obtain the title compound (210 mg, 0.64 mmol, 64%).

(f) 3-(2-Hydroxyethyl)-3-trimethylsilyloxy-1-azabicyclo [2.2.2]octane N-borane complex

[0030] Under an argon atmosphere, 3-trimethylsilyloxy-3-(2-trimethylsilyloxyethyl)-1-azabicyclo[2.2.2]octane N-borane complex (190 mg, 0.58 mmol) in anhydrous methanol (1mL) containing 0.032 M potassium carbonate in methanol (0.25 mL) was stirred at room temperature for 84 hours, acidified to pH 7 with acetic acid, and evaporated under reduced pressure. Purification by flash chromatography (eluting with hexane/ethyl acetate, 3:2) provided the title compound (94 mg, 0.37 mmol, 63%)

(g) 3-(2-Methanesulfonyloxyethyl)-3-trimethylsilyloxy-1-azabicyclo[2.2.2]octane N-borane complex

[0031] Under an argon atmosphere, methanesulfonyl chloride (0.086 mL, 1.1 mmol) in anhydrous pyridine (1 mL) was added over 20 minutes at 0°C - 5°C to a solution of 3-(2-hydroxy-ethyl)-3-trimethylsilyloxy-1-azabicyclo[2.2.2]octane N-borane complex (257 mg, 1 mmol) in anhydrous pyridine (4 mL), stirred at 0°C for 20 minutes, and at room temperature for 2 hours. Poured into ice (15 g), extracted four times with ethyl acetate, combined the organic layers, and washed sequentially with 1 N aqueous hydrochloric acid (three times), water, and saturated aqueous sodium bicarbonate. The extracts were dried ($MgSO_4$), evaporated under reduced pressure and purified by flash chromatography (eluting with chloroform/ethyl acetate, 97:3) to obtain the title compound (263 mg, 0.78 mmol, 78%).

Preparation 5

(a) 3-Ethenyl-3-hydroxy-1-azabicyclo[2.2.2]octane

[0032] Under an argon atmosphere, a solution of 3-quinuclidinone (1.25 g, 10 mmol) in anhydrous tetrahydrofuran (10 mL) was added over 15 minutes to a 1 M solution of vinylmagnesium bromide in tetrahydrofuran (20 mL, 20 mmol) at 0°C to 5°C , stirred at room temperature for 24 hours. cooled to 0°C, and acidified to pH 1 with 6 M hydrochloric acid. The mixture was stirred for 15 minutes, basified to pH 10 with 25% aqueous sodium hydroxide, extracted with chloroform (4 x 50 mL) and chloroform/methanol (4:1, 50 mL), combined the organic layers, dried ($MgSO_4$), evaporated under reduced pressure and purified by flash chromatography (eluting with ammoniated chloroform/methanol, 85:15) to obtain the title compound (830 mg, 5.4 mmol, 54%).

(b) 3-Bromo-2-hydroxypyridine

[0033] A solution of bromine (9.6 g, 60 mmol) in 1 M aqueous potassium bromide (120 mL) was added over 5 minutes to a solution of 2-hydroxypyridine (5.7 g, 60 mmol) in 1 M aqueous potassium bromide (60 mL) and stirred for 24 hours. The solid precipitate was filtered off, the aqueous phase was saturated with sodium chloride and extracted with chloroform (4 x 20 mL), the combined extracts were dried ($MgSO_4$), evaporated under reduced pressure and combined with the original precipitate. Purification by flash chromatography (eluting with ammoniated chloroform/methanol, 95:5) and recrystallization from acetonitrile provided the title compound (3.62 g, 20.8 mmol, 35%).

(c) 3-Bromo-2-methoxypyridine

[0034] Under an argon atmosphere, a mixture of 3-bromo-2-hydroxypyridine (3.49 g, 20 mmol), silver carbonate (3.67 g, 13.31 mmol), and iodomethane (1.5 mL, 24.1 mmol) in benzene (30 mL) was stirred in the dark at 40°C to 50°C for 24 hours, cooled in an ice bath, and filtered. The filtrate was washed once with 2% aqueous sodium bicarbonate and twice with water, dried ($MgSO_4$), the benzene was evaporated at atmospheric pressure, and the residue was purified by flash chromatography (eluting with hexane/ethyl acetate, 2:1) to obtain the title compound (2.35 g, 12.5 mmol, 62%).

Example 1

Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b] pyridine]

[0035] 5'-Spiro[1-azabicyclo[2.2.2]octane-3,2'(3'H)-furo[2,3-b]pyridine] N-borane complex (12.2 g, 53 mmol) was dissolved in 150 mL of acetone, the solution was cooled to 0°C, and an aqueous solution of HBr (24%; 50 mL) was added. The resulting solution was stirred at room temperature under nitrogen for 24 hours. The reaction was concentrated under reduced pressure, and the aqueous residue was treated with saturated aqueous sodium carbonate solution (50 mL). The solution was basified to pH >10 using solid sodium carbonate, and the resulting solution was extracted with chloroform (3 x 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to afford the title compound (11.2 g, 51.8 mmol, 98%, 54% overall) as an off-white solid: electrospray MS 217 ($[MH]^+$, 72).

[0036] The title compound was separated into its (R)- and (S)-enantiomers by either of the following methods:

Method A - 250 mg of the title compound was separated by chiral HPLC, using a 2cm X 25cm CHIRALCEL-OD column on a Waters Delta Prep 3000 Preparative Chromatography System, eluting with 2,2,4-trimethylpentane/ethanol (92:8 to 9:1) at a flow rate of 20 mL/min. This provided 111 mg of the (S)-enantiomer ($[\alpha]^{23} = +59.7°$ (c = 1, methanol)) and 90 mg of the (R)-enantiomer ($[\alpha]^{23} = -63.9°$ (c = 1, methanol)).

Method B - 1 g (4.62 mmol) of the title compound was treated with L-(+)-tartaric acid (694 mg; 4.62 mmol) in 15 % aqueous ethanol (10 mL) and recrystallized three times to obtain the (S)-enantiomer L-(+)-tartrate (650 mg; 1.77 mmol; $[\alpha]^{23} = +57.7°$ (c = 2, H_2O)). The filtrates were concentrated under reduced pressure and the aqueous residue was basified to pH >10 using solid sodium carbonate. The resulting mixture was extracted with chloroform (3 x 25 mL) and the combined extracts were dried ($MgSO_4$), and evaporated under reduced pressure. The residue (650 mg; 3 mmol) was treated with D-(-)-tartaric acid (452 mg; 3 mmol) and recrystallized as above to provide the (R)-enantiomer D-(-)-tartrate (775 mg; 2.11 mmol; $[\alpha]^{23} = -58.2°$ (c = 2, H_2O)).

Claims

1. (*R*)-Spiro[1-azabicyclo[2.2.2]octane-3,2'-(3'H)-furo [2,3-b]pyridine] tartrate.

2. A compound as defined in claim 1, for use in therapy.

3. A pharmaceutical composition including a compound as defined in claim 1, in admixture with an inert pharmaceutically acceptable diluent or carrier.

4. The pharmaceutical composition according to claim 3, for use in the treatment or prophylaxis of human diseases or conditions in which activation of an α7 nicotinic receptor is beneficial.

5. The pharmaceutical composition according to claim 3, for use in the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

6. The pharmaceutical composition according to claim 3, for use in the treatment or prophylaxis of Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder, anxiety, schizophrenia, or mania or manic depression Parkinson's disease, Huntington's disease, Tourette's syndrome, neurodegenerative disorders in which there is loss of cholinergic synapse, jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for ulcerative colitis.

7. Use of a compound as defined in claim 1, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which activation of an α7 nicotinic receptor is beneficial.

8. The use of a compound as defined in claim 1, in the manufacture of a medicament for the treatment or prophylaxis of psychotic disorders or intellectual impairment disorders.

9. The use according to claim 8, wherein the psychotic or intellectual impairment disorder is Alzheimer's disease, learning deficit, cognition deficit, attention deficit, memory loss, Attention Deficit Hyperactivity Disorder.

10. The use according to claim 8, wherein the psychotic or intellectual impairment disorder is anxiety, schizophrenia, or mania or manic depression.

11. The use according to claim 8, wherein the psychotic or intellectual impairment disorder is Parkinson's disease, Huntington's disease, Tourette's syndrome, or neurodegenerative disorders in which there is loss of cholinergic synapses.

12. The use of a compound as defined in claim 1, in the manufacture of a medicament for the treatment or prophylaxis of jetlag, cessation of smoking, nicotine addiction including that resulting from exposure to products containing nicotine, pain, and for ulcerative colitis.

Patentansprüche

1. (*R*)-Spiro[1-azabicyclo[2.2.2]octan-3,2'-(3'H)-furo [2,3-b]pyridin]tartrat.

2. Verbindung nach Anspruch 1 zur Verwendung in der Therapie.

3. Pharmazeutische Zusammensetzung, enthaltend eine wie in Anspruch 1 definierte Verbindung in einer Mischung mit einem inerten, pharmazeutisch annehmbaren Verdünnungsmittel oder Trägerstoff.

4. Pharmazeutische Zusammensetzung nach Anspruch 3 zur Verwendung bei der Behandlung oder Prophylaxe von Erkrankungen bzw. Leiden des Menschen, bei denen eine Aktivierung des nikotinischen α7-Rezeptors von Vorteil ist.

5. Pharmazeutische Zusammensetzung nach Anspruch 3 zur Verwendung bei der Behandlung oder Prophylaxe von psychotischen Störungen oder Intelligenzstörungen.

6. Pharmazeutische Zusammensetzung nach Anspruch 3 zur Verwendung bei der Behandlung oder Prophylaxe von Alzheimer-Krankheit, Lernschwäche, Denkschwäche, Aufmerksamkeitsschwäche, Gedächtnisverlust, hyperkinetischem Syndrom, Angstzuständen, Schizophrenie, Manie oder manischer Depression, Parkinson-Krankheit, Chorea Huntington, Tourette-Syndrom, neurodegenerativen Erkrankungen mit Verlust cholinerger Synapsen, Jet-Lag, Rauchentwöhnung, Nikotinabhängigkeit einschließlich einer Nikotinabhängigkeit, die von nikotinhaltigen Produkten herrührt, Schmerzen und Colitis ulcerosa.

7. Verwendung einer wie in Anspruch 1 definierten Verbindung bei der Herstellung eines Medikaments zur Behandlung oder Prophylaxe von Erkrankungen oder Leiden des Menschen, bei denen eine Aktivierung des nikotinischen α7-Rezeptors von Vorteil ist.

8. Verwendung einer wie in Anspruch 1 definierten Verbindung bei der Herstellung eines Medikaments zur Behandlung oder Prophylaxe von psychotischen Störungen oder Intelligenzstörungen.

9. Verwendung nach Anspruch 8, wobei es sich bei dem Leiden bzw. der Störung um Alzheimer-Krankheit, Lernschwäche, Denkschwäche, Aufmerksamkeitsschwäche, Gedächtnisverlust oder hyperkinetisches Syndrom handelt.

10. Verwendung nach Anspruch 8, wobei es sich bei der Störung um Angstzustände, Schizophrenie oder Manie oder manische Depression handelt.

11. Verwendung nach Anspruch 8, wobei es sich bei der Störung um Parkinson-Krankheit, Chorea Huntington, Tourette-Syndrom oder neurodegenerative Erkrankungen mit Verlust cholinerger Synapsen

handelt.

12. Verwendung einer wie in Anspruch 1 definierten Verbindung bei der Herstellung eines Medikaments zur Behandlung oder Prophylaxe von Jet-Lag, Rauchentwöhnung, Nikotinabhängigkeit einschließlich einer Nikotinabhängigkeit, die von nikotinhaltigen Produkten herrührt, Schmerzen und Colitis ulcerosa.

Revendications

1. (*R*)-spiro[1-azabicyclo[2,2,2]octane-3,2'-(3'H) furo-[2,3-b]pyridine]tartrate.

2. Composé tel que défini dans la revendication 1, destiné à être utilisé en thérapie.

3. Composition pharmaceutique comprenant un composé tel que défini dans la revendication 1, en mélange avec un diluant ou un support inerte pharmaceutiquement acceptable.

4. Composition pharmaceutique selon la revendication 3, destinée à être utilisée pour le traitement ou la prophylaxie de maladies ou d'affections humaines pour lesquelles une activation d'un récepteur nicotinique α7 est bénéfique.

5. Composition pharmaceutique selon la revendication 3, destinée à être utilisée pour le traitement ou la prophylaxie de troubles psychotiques ou de troubles de déficit intellectuel.

6. Composition pharmaceutique selon la revendication 3, destinée à être utilisée pour le traitement ou la prophylaxie de la maladie d'Alzheimer, du déficit d'apprentissage, du déficit de cognition, du déficit d'attention, de la perte de la mémoire, du trouble d'hyperactivité déficitaire de l'attention, de l'anxiété, de la schizophrénie, ou de la manie ou de la dépression maniaque, de la maladie de Parkinson, de la maladie de Huntington, du syndrome de Tourette, de troubles neurodégénératifs pour lesquels il existe une perte de synapse cholinergique, du décalage horaire, de l'arrêt de fumer, de la nicotinomanie y compris celle résultant de l'exposition à des produits contenant de la nicotine, de la douleur et pour la rectocolite hémorragique.

7. Utilisation d'un composé tel que défini dans la revendication 1, pour la fabrication d'un médicament destiné au traitement ou à la prophylaxie de maladies ou d'affections humaines pour lesquelles une activation d'un récepteur nicotinique α7 est bénéfique.

8. Utilisation d'un composé tel que défini dans la revendication 1, pour la fabrication d'un médicament destiné au traitement ou à la prophylaxie de troubles psychotiques ou de troubles de déficit intellectuel.

9. Utilisation selon la revendication 8, dans laquelle le trouble psychotique ou de déficit intellectuel est la maladie d'Alzheimer, le déficit d'apprentissage, le déficit de cognition, le déficit d'attention, la perte de la mémoire, le trouble d'hyperactivité déficitaire de l'attention.

10. Utilisation selon la revendication 8, dans laquelle le trouble psychotique ou de déficit intellectuel est l'anxiété, la schizophrénie, ou la manie ou la dépression maniaque.

11. Utilisation selon la revendication 8, dans laquelle le trouble psychotique ou de déficit intellectuel est la maladie de Parkinson, la maladie de Huntington, le syndrome de Tourette ou des troubles neurodégénératifs pour lesquels il existe une perte de synapses cholinergiques.

12. Utilisation d'un composé tel que défini dans la revendication 1, pour la fabrication d'un médicament destiné au traitement ou à la prophylaxie du décalage horaire, de l'arrêt de fumer, de la nicotinomanie y compris celle résultant de l'exposition à des produits contenant de la nicotine, de la douleur et pour la rectocolite hémorragique.